REMARKS/ARGUMENTS

Claims 1-7 are pending. Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Rejection under 35 USC § 112 first paragraph

Claims 1-4 and 5-7 stand rejected under 35 USC 112 first paragraph as allegedly lacking enablement. This rejection is respectfully traversed.

The Examiner argues that the currently amended scope of solvents are:

> "the alcohol is selected from the group consisting of methanol, ethanol, isopropyl alcohol, tert-butyl alcohol and n-butyl alcohol and the chlorinated solvent is selected from the group consisting of chloroform, methylene dichloride, carbon tetrachloride and ethylene dichloride"

in any combination or any ratio without limitation. The Examiner argues that there are two examples using methanol/chloroform in 50/50 v/v ratio and ethanol/chloroform in 60/50 v/v ratio, and that such limited exemplification does not warrant the claimed scope since it was provided in the record the O'Hara reference, that one having ordinary skill in the art would recognized that "optimization" of solvent evaporation is an "unpredictable" parameter. The Examiner argues that the Attorney provided no factual support that the narrow variation (methanol and ethanol) and narrow ratio can predict such claimed scope of unlimited choices of mixing and ratio of all the solvents.

However, the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. United States v. Telectronics, Inc., 857 F.2d 778, 785 (Fed. Cir. 1988). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 USC 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. In re Marzocchi, 439 F.2d 220, 224 (CCPA 1971).

Here, the claims are enabled because there is not any reason to doubt the objective truth of the statements contained in the Specification for enabling support. The Specification discloses

the manner and process for making and using the claimed invention, including working examples which show the efficacy of the claimed invention.

The Specification discloses a method wherein donepezil hydrochloride is dissolved in the mixture of methanol and chloroform and the solution is subjected to vacuum drying to give amorphous donepezil hydrochloride (see Example 1, ¶[0011]), and further discloses subjecting the solution to spray drying instead of vacuum drying using nitrogen gas to give amorphous donepezil hydrochloride (see Example 2, ¶[0012]). The Specification further discloses crystalline donepezil hydrochloride dissolved in a mixture of ethanol and chloroform and this solution is subjected to vacuum drying to give amorphous donepezil hydrochloride (see Example 3, ¶[0013]) and further discloses subjecting the solution to spray drying instead of vacuum drying using nitrogen gas to give amorphous donepezil hydrochloride (see Example 4, ¶[0014]). Thus, the ordinarily skilled artisan would have been able to make and use/practice the claimed method without undue experimentation at the time of filing.

The Examiner argues that the scope of the solvents is in any combination or any ratio without limitation. However, there are limitations on the mixture of solvents because the claims are directed to methods which produce amorphous donepezil hydrochloride. The Specification provides sufficient teaching for one of skill in the art to practice the claimed methods, and the limitation on the mixture is that the mixture used in the process produces amorphous donepezil hydrochloride.

Thus, given the teachings of the Specification, the quantity of experimentation required is not excessive in view of the subject matter of the claims. The Specification sets forth several methods for producing amorphous donepezil hydrochloride. Working Examples are provided, including working examples of spray drying, as well as detailed information as to the methods. This information can be used by one of ordinary skill in the art to determine appropriate solution conditions to practice the claimed process, without undue experimentation.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 USC § 102

Claims 1 and 4 stand rejected under 35 USC 102(e) over Vidyadhar et al. (U.S. Patent No. 6,649,765). This rejection is respectfully traversed.

In Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051,

1053 (Fed. Cir. 1987) (MPEP 2131), the CAFC set forth that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference". In the instant case, not every element of the claims is present in the '765 Vidyadhar patent.

The claims are directed to a process for preparation of amorphous donepezil hydrochloride, which comprises dissolving donepezil hydrochloride in a mixture of an alcohol and a chlorinated solvent; and removing the solvents from the solution; wherein the alcohol is selected from the group consisting of methanol, ethanol, isopropyl alcohol, tert-butyl alcohol and n-butyl alcohol and the chlorinated solvent is selected from the group consisting of chloroform, methylene dichloride, carbontetrachloride and ethylene dichloride.

In contrast, the '765 Vidyadhar patent discloses preparing donepezil free base in methylene chloride, then removing the methylene chloride (see Example 2). In an additional step, the donepezil free base is dissolved in methanol, followed by addition of hydrochloric acid. Thus, there is not a disclosure in the '765 Vidyadhar patent of a process wherein donepezil hydrochloride dissolved in a mixture of an alcohol and a chlorinated solvent.

The Examiner argues that it is well recognized in the chemical art that methanol and methylene dichloride are material that will be fully miscible with organic solvents (citing Merck Index #5814 methanol "miscible with most organic solvents", #5932 methylene chloride "miscible with alcohol"), and that such miscible solvents whether mixed in situ or pre-mixed would not be different since they are miscible with each other. The Examiner argues that Applicants provided no factual evidence that why the pre-mixed methanol/methylene chloride and the in situ mixed methanol/methylene chloride would be different as to be not inherently mixture of the two material.

However, there is no teaching in '765 Vidyadhar of a mixture of methylene dichloride with methanol. While the Merck index may teach that methylene chloride is miscible with alcohols, there is no teaching in the Merck index or '765 Vidyadhar that such solvents should be mixed together and used in a process to produce amorphous donepezil.

In addition, there is not a reasonable expectation that different solvents would result in the formation of amorphous donepezil hydrochloride because it is known in the art that the use of different solvents will produce different crystalline forms of a product. For example, U.S. Patent

Application Publication No. 2004/0102523 (Broquaire et al.) is directed to a process for obtaining crystalline forms of the enantiomers of modafinil, and the crystalline forms which it is possible to obtain according to this process. The '523 publication discloses that ¶[0109]:

> "[i]n this method, the nature of the solvent selected and the conditions of crystallization selected can be used to direct the preparation of any of the polymorphic forms. Crystallization solvents and conditions will be disclosed hereinafter for each modafinil form, respectively I, III, IV and VII obtained according to this method".

Furthermore, Banga et al. teaches (Banga S, Chawla G, Bansal AK. New trends in crystallization of active pharmaceutical ingredients. Business Briefing: Pharmagenerics 2004, 1-5 (Nov)) (pages 2-3):

> The concept that different crystalline modifications arise under varied experimental conditions demands the use of a diverse medley of crystallisation approaches to explicate the polymorph spectrum. Currently, the polymorph screen is a jumbled affair based mostly upon hit and trial bases. Crystallisation from solution (single solvent or solvent mixtures) and non-solvent methods such as sublimation, thermal treatment, desolvation, processing (grinding) and crystallisation from melting are the commonly used traditional approaches for polymorph screening. A meticulous consideration of the factors of solvent recrystallisation like solvent polarity, degree of supersaturation, temperature along with the cooling profile, additives, seeds, pH and agitation rate aids in elucidating the complete polymorphic picture of the drug.[9] However, the traditional crystallisation methods are exhausting, time-consuming and may be liable to miss metastable forms having an energy difference of less than 10kJ/mole, as observed in the case of paracetamol and chlorthalonil.[5] Therefore, innovative techniques allowing generations of 'crystal mutants' would prove to be of high value.

Therefore, the assumption that crystallization from a mixture of an alcohol and a chlorinated solvent will yield the same amorphous form as crystallization from methylene chloride alone, followed by a step wherein the donepezil free base is dissolved in methanol, followed by addition of hydrochloric acid, as in Vidyadhar '765 patent has no basis in fact.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 USC § 103

Claims 1-4, 5-7 stand rejected under 35 USC 103(a) over Vidyadhar '765 in view of Imai '864 or over Sugimoto '841 or Vidyadhar '765 or Imai '864 in view of Lieberman and Brittain.

This rejection is respectfully traversed.

The Examiner argues that Sugimoto et al. (col. 34 example 4) or Vidyadhar et al. '765 (col. 4, example 2) disclosed process of making donepezil hydrochloride of the claims. Imai et al. '864 disclosed multiple variations of modifying the process of making donepezil hydrochloride to obtain variations of crystalline and pure forms of the compound. The Examiner admits that the difference between the prior art processes and the instant claimed process is that the products being made are crystalline or solids; using mixtures of more limited solvent combinations; and/or the method of solvent removal being particularly vacuum drying or spray drying. The Examiner argues that it is conventionally known that donepezil hydrochloride is soluble in a variety of solvents (see Imai et al. '864 entire document). The Examiner argues that it is a conventional teaching that amorphous is more desirable than crystalline form when formulation into pharmaceutical compositions (see Lieberman p.463 last paragraph) and the conventional process for obtaining amorphous material are spray drying or vacuum drying i.e. lyophilization. The Examiner argues that one having ordinary skill in the art in possession of Sugimoto '841 or Vidyadhar '765 and the above references by Imai et al. '864, Lieberman and Brittain would be in possession of the instant claims because a proven process of making donepezil hydrochloride in a purified form was disclosed by Sugimoto '841, Vidyadhar '765 or Imai '864.

However, the claims are patentable over the combination of Vidyadhar '765 in view of Imai '864 or over Sugimoto '841 or Vidyadhar '765 or Imai '864 in view of Lieberman and Brittain for the following reasons. The framework for the objective analysis for determining obviousness under 35 U.S.C. 103 is stated in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows: (A) Determining the scope and content of the prior art; and (B) Ascertaining the differences between the claimed invention and the prior art; and (C) Resolving the level of ordinary skill in the pertinent art. To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385 (CCPA 1970). MPEP 2143.03. It is important to identify a reason that would have prompted a

person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. (KSR v Teleflex, 12 S.Ct. 1727, 1740 (US 2007)). In the instant case, not every element of the claims is taught or suggested in the combination of Vidyadhar '765 in view of Imai '864 or over Sugimoto '841 or Vidyadhar '765 or Imai '864 in view of Lieberman and Brittain.

Here, the claims are directed to a process for preparation of amorphous donepezil hydrochloride, which comprises dissolving donepezil hydrochloride in a mixture of an alcohol and a chlorinated solvent; and removing the solvents from the solution; wherein the alcohol is selected from the group consisting of methanol, ethanol, isopropyl alcohol, tert-butyl alcohol and n-butyl alcohol and the chlorinated solvent is selected from the group consisting of chloroform, methylene dichloride, carbontetrachloride and ethylene dichloride.

Claim 1 recites that the process "comprises dissolving donepezil hydrochloride in a mixture of an alcohol and a chlorinated solvent". This limitation is clearly not disclosed in the '765 Vidyadhar patent. As set forth above, the '765 Vidyadhar patent discloses preparing donepezil free base in methylene chloride, then removing the methylene chloride (see Example 2). In an additional step, the donepezil free base is dissolved in methanol, followed by addition of hydrochloric acid. Accordingly, there is not a disclosure in the '765 Vidyadhar patent of a process wherein donepezil hydrochloride dissolved in a mixture of an alcohol and a chlorinated solvent. This deficiency is not addressed by the '864 Imai patent, the Sugimoto '841 patent, or Lieberman and Brittain references.

While the '864 Imai patent discloses several polymorphs of donepezil hydrochloride, it does not teach or suggest a process for preparing amorphous donepezil hydrochloride prepared by dissolving donepezil hydrochloride in a mixture of an alcohol and a chlorinated solvent. The '864 Imai patent does not teach or suggest a chlorinated solvent which is selected from the group consisting of chloroform, methylene dichloride, carbontetrachloride and ethylene dichloride.

Furthermore, there is not a teaching or suggestion in the '841 Sugimoto patent of a process in which donepezil hydrochloride is dissolved in a mixture of an alcohol and a chlorinated solvent. Example 4 of the '841 Sugimoto patent as cited by the Examiner discloses donepezil base dissolved in methylene chloride, to which a 10% solution of hydrochloric acid in ethyl acetate is added, followed by concentration *in vacuo* to obtain a crystal, which was

recrystallized from methanol/isopropyl ether. This deficiency is not addressed by the '864 Imai patent. While the '864 Imai patent discloses several polymorphs of donepezil hydrochloride, it does not teach or suggest amorphous donepezil hydrochloride prepared by dissolving donepezil hydrochloride in a mixture of an alcohol and a chlorinated solvent. The '864 Imai patent does not teach or suggest a chlorinated solvent is chloroform, methylene dichloride, carbontetrachloride or ethylene dichloride.

The Examiner argues that Applicants are self conflicting, allegedly because on one hand applicants argued that given an example of using methanol and chloroform, the employing of other solvents is a "quantity of experimentation required is not excessive in view of the subject matter" which supports the prima facie obviousness between the prior art and the instant claims since the sole different is using various solvents of using mixture of various solvents without limitation, and the Examiner further argues that on the other hand, applicants argued that, using different solvents is not obvious because changing solvents would not be motivated.

However, Applicant is not being contradictory. The art has shown that the use of different solvents will be expected to yield different polymorphic forms here, an amorphous form. There is not a reasonable expectation that different solvents would result in the formation of amorphous donepezil hydrochloride because it is known in the art that the use of different solvents will produce different crystalline forms of a product. As set forth above, the assumption that crystallization from a mixture of an alcohol and a chlorinated solvent will yield the same polymorphic form as crystallization from methylene chloride alone, followed by a step wherein the donepezil free base is dissolved in methanol, followed by addition of hydrochloric acid, as in Vidyadhar '765 patent, has no basis in fact. The art does not teach or suggest a mixture of solvents, and thus not teach or suggest the claimed method, because no references teach the claimed mixture of solvents in a process of making amorphous donepezil.

The fact that no references teach the claimed mixture of solvents is not an issue under 35 USC 112 first paragraph, because the Specification provides sufficient direction to one of skill in the art to practice the claimed method. The claims are enabled, because the Specification exemplifies methods of making amorphous donepezil, using different mixtures of alcohol and chlorinated solvent.

In addition, there is no motivation for one of skill in the art to alter the methods of the

'841 Sugimoto patent, the '765 Vidyadhar patent, or the '864 Imai patent to arrive at the claimed method, and no reasonable expectation of success. There is no teaching or suggestion within the Lieberman and Brittain references to alter the methods as taught by the '841 Sugimoto patent, the '765 Vidyadhar patent, or the '864 Imai patent to arrive at the instantly claimed method.

In the Office Action (see page 4), the Examiner cited the recent Supreme Court decision KSR v Teleflex, 82 USPQ2d 1385 (US 2007). However, in the KSR case, the Court noted that the analysis supporting a rejection under 35 USC 103(a) should be made explicit, and that it was "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does". KSR, slip op. at 15. The Court further stated that:

> Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. See In re Kahn, 441 F. 3d 977, 988 (CA Fed. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"). KSR, slip op. at 14.

Here, there is not a combination of prior art elements, since no reference, or combination of references, teaches or suggests a process for preparing amorphous donepezil hydrochloride wherein donepezil hydrochloride is dissolved in a mixture of an alcohol and a chlorinated solvent and then the solvents are removed from the solution. No reference or combination of references teaches or suggests such a method wherein the chlorinated solvent is chloroform, methylene dichloride, carbontetrachloride or ethylene dichloride. In addition, Applicant has shown that there is not a reason why a person of ordinary skill in the art would be motivated to practice a process for preparing donepezil hydrochloride wherein donepezil hydrochloride is dissolved in a mixture of an alcohol and a chlorinated solvent and then the solvents are removed from the solution. Additionally, the Specification provides sufficient direction to one of skill in the art to practice the claimed method. Furthermore, the Examiner has not shown that there is a reason why a person of ordinary skill in the art would be motivated to substitute a mixture of an alcohol

and a chlorinated solvent for the solvents as disclosed in the cited combination of Vidyadhar '765 in view of Imai '864 or over Sugimoto '841 or Vidyadhar '765 or Imai '864 in view of the Lieberman and Brittain references. In addition, Applicant has shown that there are reasons why a person of ordinary skill in the art would not be motivated to substitute solvents, given that crystallisation methods are exhausting, time-consuming and may be liable to miss metastable forms.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

* * *

For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

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By_____
Joseph F. Murphy
Registration No. 58,313
Customer No. 03000
(215) 567-2010
Attorneys for Applicants

Please charge or credit our Account No. 03-0075 as necessary to effect entry and/or ensure consideration of this submission.